Review

Myasthenia gravis: An emerging toxicity of immune checkpoint inhibitors

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PD-1;
CTLA-4;
Autoimmunity

Abstract The advent of immunotherapy has heralded a number of significant advances in the treatment of particular malignancies associated with poor prognosis (melanoma, non-small-cell lung, renal and head/neck cancers). The success witnessed with therapeutic agents targeting cytotoxic T-lymphocyte-associated protein 4, programmed cell death protein 1 and programmed cell death ligand 1 immune checkpoints has inevitably led to an explosion in their clinical application and the subsequent recognition of specific toxicity profiles distinct from those long recognised with chemotherapy. Consequently, as the utility of such therapies broaden, understanding the nature, timing and management of these immune-related adverse events (irAEs) becomes increasingly significant. Although neurological irAEs are considered relatively rare in comparison with hepatitis, colitis, pneumonitis and endocrinopathies, one emerging side-effect is myasthenia gravis (MG). Among the 23 reported cases of immune checkpoint inhibitor-associated MG, 72.7% were de novo presentations, 18.2% were exacerbations of pre-existing MG and 9.1% were exacerbations of subclinical MG. The average onset of symptoms was within 6 weeks (range 2–12 weeks) of treatment initiation. In addition, there was no consistent association with elevated acetylcholine antibody titres and the development of immune checkpoint inhibitor-related MG. Significantly, there was a 30.4% MG-specific-related mortality, which further emphasises the importance of early recognition and robust treatment of this toxicity. In addition to a review of the existing literature, we present a new case of pembrolizumab-induced MG and provide insights into the underlying mechanisms of action of this phenomenon.

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1. Introduction

Over the past 5 years, targeted immunotherapy has created a major paradigm shift within the therapeutic landscape of numerous solid tumours. Manipulation of pathways which mediate blunting of anti-tumour immunity has predominantly focussed on the development of inhibitors directed against the immune checkpoint modulators such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1) and its ligand, PD-L1. The introduction of these novel agents has not only witnessed unprecedented extensions in survival outcomes for patients with malignant melanoma, lung, renal and head/neck cancers but reveals a plethora of immune-related toxicities for which early recognition and appropriate clinical management are paramount. Autoimmune events including hepatitis, colitis, pneumonitis, dermatitis, nephritis, endocrinopathies and hypophysitis are well-recognised phenomena which represent a manifestation of dysregulated inflammation induced by immune checkpoint inhibition. As the use of these targeted agents expand, further toxicity issues have emerged. Recently, this has been exemplified by both de novo presentations and exacerbations of pre-existing myasthenia gravis (MG) which, to date, has been reported in 22 cases in the literature. Herein, we present a new presentation of ocular MG (oMG) followed by a succinct review of cases highlighting this phenomenon.

2. De novo myasthenia gravis

2.1. Case report

An 85-year-old woman with metastatic melanoma with left axillary lymphadenopathy commenced single-agent pembrolizumab (2 mg/kg; every 3 weeks) and tolerated the first cycle without any significant toxicity. Shortly after the second cycle, she presented with diplopia that was subsequently followed by asymmetrical bilateral ptosis (L > R). The remaining neurological examination was unremarkable, and there was no evidence of oesophageal dysmotility or respiratory compromise. Brain magnetic resonance imaging (MRI) confirmed no evidence of metastatic dissemination, and both acetylcholine receptor antibodies (AChR-Abs) and anti-muscle-specific kinase antibodies (anti-MuSK Abs) were normal. In view of the high clinical suspicion of oMG, she commenced systemic treatment with intravenous immunoglobulin (IVIG; 30 g/300 mL daily for 5 d), prednisone (100 mg once daily (o.d.) for 7 d) and pyridostigmine (90 mg daily). This regimen elicited a swift clinical response with complete resolution of bilateral ptosis and diplopia. She continued a maintenance schedule of monthly IVIG and daily oral pyridostigmine without any further symptomatic recurrence. In view of the de novo presentation of oMG, pembrolizumab was discontinued, and the patient passed away shortly afterwards from unrelated cardiac issues.

3. Anti-PD-1 inhibitor-induced myasthenia gravis

In addition to this aforementioned report, since the introduction of PD-1 and PD-L1 immune checkpoint inhibitors, there have been several publications highlighting a causal relationship with the manifestation of de novo MG (Table 1).

Indeed, March et al. [1] recently documented a fatal case in a 63-year-old male with malignant melanoma of the right scalp, which had metastasised to the liver and brain, who was also treated with pembrolizumab. Two weeks after the first cycle, he presented with right ptosis, facial oedema, diplopia and dyspnoea on mild exertion. Brain MRI confirmed early response within the pre-existing brain metastases, positive AChR-Abs and negative anti-MuSK Abs. Two days after the hospitalisation, he developed progressive facial weakness, bilateral ptosis and increasing dyspnoea. Unfortunately, the presentation was refractory to appropriate intervention with pyridostigmine, high-dose steroids, IVIG and plasmapharesis, and he subsequently passed away from ventilatory failure.

Although the majority of de novo cases of MG warranted comprehensive clinical management, a select group of patients responded with comparatively minimal intervention. Gonzalez et al. [2] documented a case of a 71-year-old woman with refractory metastatic uterine carcinosarcoma who developed dysphagia, diplopia and dysarthria after four cycles of pembrolizumab. Three weeks post symptomatic onset, she developed left lateral rectus weakness, with further diplopia and ptosis (R > L). This progressed to neck extensor and proximal upper and lower limb weakness. Creatinine kinase (CK) was significantly elevated (1200 IU/l), and serology was negative for both AChR-Abs and anti-MuSK Abs. Subsequent treatment with 50-mg pyridostigmine three times daily (t.d.s.) and prednisone 20 mg o.d. alone led to a complete symptomatic response over the following 3 weeks [2]. Similarly, Nguyen et al. [3] reported two cases in patients with metastatic melanoma treated with pembrolizumab whereby minimal rescue therapy (i.e. without IVIG or plasmapharesis) resulted in a full resolution of the myasthenic symptoms. The first report highlighted a male patient who developed bilateral ptosis 5 d before the fourth cycle. Interestingly, 25-mg daily prednisone induced complete amelioration of symptoms without any delay in treatment. The second case documents a female who developed bilateral ptosis and dysphagia 7 weeks post initiation of pembrolizumab. She achieved a significant response after 10 d of the steroid therapy consisting of methylprednisolone 500 mg intravenous (i.v.) for 5 d followed by oral prednisolone slowly tapered over 4 weeks [3].
<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient</th>
<th>Pre-existing AChR status</th>
<th>Onset (weeks)</th>
<th>Cycles completed</th>
<th>Intervention</th>
<th>Elevated serum CK</th>
<th>Myasthenia-associated mortality</th>
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<tbody>
<tr>
<td><strong>Anti-PD-1 inhibitor-induced MG</strong></td>
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<tr>
<td>Case report</td>
<td>85-year-old female with metastatic melanoma treated with pembrolizumab</td>
<td>No</td>
<td>Negative</td>
<td>4.5</td>
<td>• IVIG, 450 mg/kg for 5 d &lt;br&gt; • Prednisone, 100 mg o.d. for 7 d &lt;br&gt; • Pyridostigmine, 90 mg o.d.</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Zimmer et al. [6]</td>
<td>69-year-old female with metastatic melanoma treated with pembrolizumab</td>
<td>No</td>
<td>Negative</td>
<td>9</td>
<td>• 1 g of methylprednisolone (i.v.), for 3 d then tapered to 60 mg daily &lt;br&gt; • 30 mg of pyridostigmine b.d. p.o. &lt;br&gt; • Five cycles of plasmaphaeresis</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>March et al. [1]</td>
<td>63-year-old male with metastatic melanoma treated with pembrolizumab</td>
<td>No</td>
<td>Negative</td>
<td>2</td>
<td>• Prednisone, 60 mg o.d. for 2 d escalated to 1 g methylprednisolone (i.v.) for 9 d &lt;br&gt; • 120 mg of pyridostigmine q.i.d., for 11 d &lt;br&gt; • Five treatments of IVIG at 400 mg/kg/d &lt;br&gt; • Four cycles of plasmaphaeresis</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Gonzalez et al. [2]</td>
<td>71-year-old female with uterine carcinosarcoma treated with pembrolizumab</td>
<td>No</td>
<td>Negative</td>
<td>12</td>
<td>• Pyridostigmine, 60 mg t.d.s. &lt;br&gt; • Prednisone, 20 mg o.d. &lt;br&gt; • Prednisone, 25 mg o.d. p.o.</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Nugyen et al. [3]</td>
<td>81-year-old male with metastatic melanoma treated with pembrolizumab</td>
<td>No</td>
<td>Negative</td>
<td>11</td>
<td>• 500 mg of i.v. methylprednisolone for 5 d, which was switched to prednisone on the 6th day. &lt;br&gt; • Prednisone, 60 mg p.o. o.d. &lt;br&gt; • Pyridostigmine, 60 mg t.d.s. &lt;br&gt; • IVIG, 400 mg/kg 5 d &lt;br&gt; • 45 mg q.i.d. of pyridostigmine</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Alnahhas et al. [7]</td>
<td>84-year-old female with metastatic melanoma treated with pembrolizumab</td>
<td>No</td>
<td>Positive</td>
<td>4</td>
<td>• Pyridostigmine 90 mg q.i.d. &lt;br&gt; • IVIG, 400 mg/kg for 5 d</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Polat et al. [8]</td>
<td>65-year-old male with stage IV NSCLC treated with nivolumab</td>
<td>No</td>
<td>Negative</td>
<td>8</td>
<td>• Prednisone, 60 mg p.o. o.d. &lt;br&gt; • Pyridostigmine, 60 mg t.d.s. &lt;br&gt; • IVIG, 400 mg/kg 5 d</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Sciacca et al. [9]</td>
<td>81-year-old male with stage IV NSCLC treated with nivolumab</td>
<td>No</td>
<td>Positive</td>
<td>6</td>
<td>• Pyridostigmine, 50 mg o.d. p.o.</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Chang et al. [10]</td>
<td>75-year-old male with squamous cell carcinoma of the bladder treated with nivolumab</td>
<td>No</td>
<td>Positive</td>
<td>6</td>
<td>• Pyridostigmine 90 mg q.i.d. &lt;br&gt; • IVIG, 400 mg/kg for 5 d</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Lopez et al. [11]</td>
<td>65-year-old male with renal cell carcinoma treated with nivolumab</td>
<td>No</td>
<td>Positive</td>
<td>3</td>
<td>• High-dose steroids (no further details) &lt;br&gt; • IVIG for 5 d (no dose details) &lt;br&gt; • i.v. hydration for rhabdomyolysis. &lt;br&gt; • 2 mg/kg of methylprednisolone for hepatitis. &lt;br&gt; • Nil directed therapy for MG &lt;br&gt; • Three days of steroid pulse therapy 100 mg/d followed by oral prednisolone at 1 mg/kg</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Shirai et al. [4]</td>
<td>81-year-old female with metastatic melanoma treated with nivolumab</td>
<td>Subclinical</td>
<td>Positive</td>
<td>2</td>
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<tr>
<td>Kimura et al. [5]</td>
<td>80-year-old male with metastatic melanoma treated with nivolumab</td>
<td>Subclinical</td>
<td>Positive</td>
<td>2</td>
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<tr>
<td>Study / Treatment Type</td>
<td>Patient Details</td>
<td>Outcome</td>
<td>Treatment Details</td>
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<td><strong>Anti-CTLA-4 inhibitor-induced MG</strong></td>
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<td>Liao et al. [12]</td>
<td>70-year-old female with metastatic melanoma treated with ipilimumab</td>
<td>Yes</td>
<td>Positive</td>
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<tr>
<td>Johnson et al. [13]</td>
<td>69-year-old woman with metastatic melanoma treated with ipilimumab</td>
<td>No</td>
<td>Positive</td>
<td>6 3</td>
<td></td>
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<tr>
<td>Johnson et al. [13]</td>
<td>73-year-old woman with metastatic melanoma treated with ipilimumab</td>
<td>No</td>
<td>Positive</td>
<td>3 2</td>
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<td></td>
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<td>Montes et al. [14]</td>
<td>74-year-old woman with advanced melanoma treated with ipilimumab</td>
<td>No</td>
<td>Negative</td>
<td>6 3</td>
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<tr>
<td><strong>Combination immune checkpoint inhibitor therapy-induced MG</strong></td>
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<td>Antonia et al. [15]</td>
<td>Patient with advanced NSCLC treated with durvalumab + tremelimumab</td>
<td>Unknown</td>
<td>Unknown</td>
<td>2 1</td>
<td></td>
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<tr>
<td>Loochtan et al. [16]</td>
<td>70-year-old male with extensive stage SCLC treated with nivolumab + ipilimumab</td>
<td>No</td>
<td>Positive</td>
<td>2 2</td>
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<tr>
<td><strong>PD-1 inhibitor exacerbation of MG</strong></td>
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<td>Lau et al. [18]</td>
<td>75-year-old male with metastatic melanoma treated with pembrolizumab</td>
<td>Yes</td>
<td>Positive</td>
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<tr>
<td>Zhu et al. [21]</td>
<td>59-year-old with metastatic melanoma treated with pembrolizumab</td>
<td>Yes</td>
<td>Negative</td>
<td>9 3</td>
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<tr>
<td>Phadke et al. [20]</td>
<td>75-year-old male with metastatic melanoma treated with pembrolizumab</td>
<td>Yes</td>
<td>Positive</td>
<td>6 2</td>
<td></td>
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<tr>
<td>Maeda et al. [19]</td>
<td>79-year-old male with metastatic melanoma treated with nivolumab</td>
<td>Yes</td>
<td>Positive</td>
<td>9 3 before the event and 7 post the event</td>
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</tbody>
</table>

**AChR**, acetylcholine receptor; MG, myasthenia gravis; CK, creatinine kinase; PD-1, programmed cell death 1; IVIG, intravenous immunoglobulin; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; i.v., intravenous; o.d., once daily; b.d., twice daily; t.d.s., three times daily; q.i.d., four times daily; p.o., oral administration.
Significantly, all of the seven reported cases of nivolumab-associated MG occurred within a relatively short timeframe (2–9 weeks) from drug initiation (Table 1). A case reported by Shirai et al. [4] lucidly highlights the swift deterioration of an 81-year-old woman with metastatic melanoma who developed mild fatigue and proximal limb weakness within the 2 weeks of commencing nivolumab. Nine days later, she developed bilateral ptosis and diplopia with worsening dyspnoea and muscle weakness. The clinical picture combined with positive AChR-Abs strongly indicated nivolumab-induced MG. Despite the availability of IVIG and ventilatory support, the patient declined any further measures and passed away 27 d after the initial dose of nivolumab. Interestingly, a retrospective study of the patient’s serum before nivolumab administration also demonstrated positive AChR-Abs, unearthing a prior subclinical serological MG [4].

Similarly, Kimura et al. [5] also documented a case in which an 80-year-old male with metastatic melanoma being treated with nivolumab was found retrospectively to have subclinical MG, which was exposed as a result of PD-1 therapy. This patient presented with severe dyspnoea and muscle weakness requiring intubation 2 weeks after the first dose of nivolumab. The severity of his disease warranted intensive treatment including steroid pulse therapy (1000 mg/d), prednisone (1 mg/kg tapered to 20 mg/d on normalisation of serum CK levels), plasma exchange, IVIG (400 mg/kg/d) and low-dose pyridostigmine. After 4 months of treatment in intensive care, he was able to be rehabilitated on a general medical ward [5].

In addition to these notable cases, the literature reveals six further cases of PD-1 inhibitor-induced MG summarised herein:

- Zimmer et al. [6] reported a case of a 69-year-old woman who developed MG after treatment with pembrolizumab for metastatic melanoma of the vulva. Despite treatment with methylprednisolone, plasmapheresis and pyridostigmine, she deteriorated and as a result passed away 4 months later.
- Almahhas et al. [7] presented a case of an 84-year-old man who developed MG after treatment with pembrolizumab for metastatic melanoma. He developed dysphagia and bilateral ptosis and had a significant clinical response to prednisone, IVIG and pyridostigmine.
- Polat et al. [8] documented a case of a 65-year-old man who developed MG after treatment with nivolumab for stage IV non-small-cell lung cancer (NSCLC). He developed bilateral ptosis and diplopia which responded to pyridostigmine alone.
- Sciacca et al. [9] also presented a case of an 81-year-old man who developed MG after treatment with nivolumab for stage IV NSCLC. He presented with bilateral ptosis and proximal limb weakness and responded well to prednisone alone.
- Chang et al. [10] reported a case of a 75-year-old man who developed MG after treatment with nivolumab for squamous cell carcinoma of the bladder. He presented with bilateral ptosis, generalised weakness, dysphagia and dyspnoea, which improved with IVIG and pyridostigmine.
- Lopez et al. [11] documented a case of a 65-year-old man who developed MG after treatment with nivolumab for advanced renal clear cell carcinoma. He presented with dyspnoea, diplopia and progressive muscle weakness. Despite treatment with IVIG and high-dose steroids, he developed respiratory failure and subsequently passed away.

### 4. Anti-CTLA-4 inhibitor-induced myasthenia gravis

To date, there have been four cases of MG with the anti-CTLA-4 antibody, ipilimumab; all of which have been de novo presentations [12–14]. Intriguingly, all cases occurred within 6 weeks of initiation of ipilimumab and were not associated with any mortality. Liao et al. [12] reported a case of a 70-year-old female with uveal melanoma and liver metastases who was commenced on ipilimumab. After the second infusion, she developed generalised myalgia, dysphagia, odynophagia, bilateral ptosis, fatigability and weakness of neck flexion and extension and proximal muscle weakness in all limbs. Repetitive nerve stimulation demonstrated mild postsynaptic neuromuscular junction dysfunction suggestive of MG. Serology revealed an elevated CK (1200 IU/l) and a raised AChR-Abs titre of 2.09 nmol/l (normal <0.3 nmol/l). She was diagnosed with a myositis and MG syndrome and commenced plasmapheresis and methylprednisolone with a significant clinical response which was maintained with monthly IVIG and low-dose pyridostigmine [12].

Interestingly, two patients treated with anti-CTLA-4 agents developed pruritus and a rash before the development of MG. Johnson et al. [13] reported a case of a 69-year-old woman with melanoma on her right lower extremity which progressed with numerous subcutaneous metastases and fluorodeoxyglucose (FDG)-avid inguinal and popliteal lymphadenopathy confirmed on positron emission tomography scanning. Consequently, she was commenced on a dose of 3 mg/kg of ipilimumab every 3 weeks. After her first cycle, she developed a mild rash and pruritus at the primary melanoma resection site. After the third cycle of ipilimumab, she developed bilateral ptosis, diplopia and dysphagia to solid foods. Electromyography was consistent with a postsynaptic neuromuscular junction disorder and AChR-Abs were elevated. As a result, she was commenced on pyridostigmine (30 mg t.d.s.). Despite this, she continued to deteriorate with worsening dysphagia, fatigable weakness, mild shortness of breath and an inability to extend her neck. The treatment was then escalated to include i.v. methylprednisolone (2 mg/kg) and plasmapheresis resulting in a gradual symptom reduction [13]. In addition to this case, Johnson et al. [13] also report a case of a 73-year-old woman who developed MG after treatment with ipilimumab for metastatic melanoma. She
developed dyspnoea and proximal limb weakness yet responded well to high-dose corticosteroids and pyridostigmine [13].

Similarly, Montes et al. [14] described a case of a 74-year-old male with advanced melanoma who was treated with ipilimumab. After the second cycle, he developed a mild rash and pruritus. After the third cycle, he developed dyspnoea, diplopia and fatigable weakness on examination. Serology for AChR-Abs was negative, yet a Tensilon test and repetitive nerve stimulation study were consistent with MG. Treatment with pyridostigmine and prednisone resulted in a complete resolution of all the symptoms except for diplopia [14]. Given the small sample size of four patients with ipilimumab-induced MG, it is difficult to assess the relationship between the development of a rash/pruritus and MG.

5. Combination immune checkpoint inhibitor therapy-induced myasthenia gravis

Currently, there are two reports of combination immune checkpoint inhibitor therapy inducing MG. The first case by Antonia et al. [15] notes a patient who received durvalumab (anti-PD-L1 inhibitor; 10 mg/kg) and tremelimumab (anti-CTLA-4 inhibitor; 1 mg/kg) delivered on a 4-week schedule [15]. The patient was diagnosed with advanced NSCLC and developed MG within 10 d of initiating treatment. Unfortunately, there is a paucity of further information on the patient profile and treatment history with the only other detail limited to the mortality associated with this particular case. The second is documented by Loochtan et al. [16] who report a case of a 70-year-old male with extensive stage small-cell lung cancer (enrolled into the phase I/II CheckMate 032 study [17]) receiving nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) who developed ptosis and diplopia 16 d post initiation of immune checkpoint inhibition. Despite treatment with IVIG, plasmaphaeresis and steroids, he deteriorated requiring intubation. The exact cause of death is unknown as the patient concurrently developed complete heart block, sepsis and a perforated duodenal ulcer. Yet given the lack of response to the appropriate therapy, MG is likely to have played a role in this patient’s demise.

6. PD-1 inhibitor exacerbation of myasthenia gravis

In addition to de novo MG, there have been four such reports [18–21] of patients with exacerbations of pre-existing MG as a direct consequence of immune checkpoint inhibition.

One such case reported by Lau et al. [18] documents a 75-year-old man, with a known history of non-thymomatous AChR-Ab positive generalised MG maintained on azathioprine, who was diagnosed with metastatic melanoma. Two weeks after the second cycle of pembrolizumab, he presented with ataxia, neck weakness and ptosis. Notably, 3 weeks before his presentation, tapering of his azathioprine was commenced in view of the hepatotoxicity induced by the concomitant treatment with pembrolizumab. He commenced methylprednisolone (1 g daily; 5 d) and IVIG (0.5 mg/kg daily; 4 d). This resulted in a complete resolution of facial and neck flexor weakness with only subtle proximal upper extremity weakness persisting. After complete resolution of his symptoms, he was maintained with monthly IVIG (2 mg/kg).

Maeda et al. [19] documented a case of a 79-year-old man with metastatic melanoma who was commenced on nivolumab for management of his submandibular lymph node metastasis. This patient had a 20-year history of oMG maintained on oral corticosteroids (3 mg; alternate days). Nine weeks after the drug initiation, he presented with diplopia, facial muscle weakness and dysphagia with fluids. Positive serum AChR-Abs in addition to these symptoms supported the diagnosis of exacerbated MG. Significantly, rescue therapy with pyridostigmine, IVIG or plasmaphaeresis was not required. Furthermore, the patient continued his normal dose of corticosteroids with swift symptomatic resolution and continued with seven further cycles of nivolumab without recurrent issues.

Alongside these cases, the literature contains two further reports of PD-1-exacerbated MG as summarised herein:

- Zhu et al. [21] reported a case of a 59-year-old woman who experienced the exacerbation of MG induced by pembrolizumab therapy for metastatic melanoma. She presented with rapidly progressive dysphonia and dysphagia requiring the insertion of a percutaneous endoscopic gastrostomy tube. She was managed with plasmaphaeresis, IVIG and prednisone resulting in a steady improvement of her symptoms [21].

- Phadke et al. [20] also documented a case of a 75-year-old man with the exacerbation of MG caused by pembrolizumab therapy for metastatic melanoma. Owing to concerns of the possible drug toxicities, he underwent a dose reduction of his mycophenolate mofetil, used to control his MG. He subsequently presented with dysphagia and respiratory distress warranting gastrostomy tube placement and non-invasive ventilation, respectively. His symptoms responded well with plasma exchange, IVIG, rituximab, pyridostigmine and prednisone [20].

7. Discussion

Historically, the excitement generated by the introduction of novel therapies within the treatment armament for oncology patients is also moderated by the emergence of an often unique constellation of toxicities which require prompt recognition and robust clinical management. This is particularly emphasised by the immune-related adverse events (irAEs) associated with
immune checkpoint inhibitors. Zimmer et al. [6] published a study of 496 patients being treated with anti-PD-1 therapy in which there were a total of 242 irAEs in 138 patients. These side-effects ranged from respiratory (17.3%), musculoskeletal (15.2%), neurological (11.5%), ocular (5.7%), cardiac (3.6%) and haematological (0.7%). Moreover, with approximately one-third of patients experiencing significant toxicities, it emphasises that constant vigilance must be undertaken by the prescribing physician. Indeed, as the use of these agents increase, less common side-effects with potentially fatal consequences inevitably fall under the spotlight. In contrast to the Zimmer et al. study, neurological sequelae (e.g. MG, Guillain-Barre Syndrome, posterior reversible leukoencephalopathy, Bell’s palsy) with immune checkpoint inhibitors are considered rare events [22]. With respect to the 23 reported cases of irAEs manifesting as MG (Table 1), the specific MG-related mortality of 30.4% reported in this review highlights the importance in recognising this as a significant toxicity that warrants attention. Interestingly, none of the cases of ipilimumab-induced MG were associated with mortality, yet conversely, both cases of immune checkpoint inhibitor combination therapy were associated with MG-related death.

Of these presentations, 72.7% were de novo, 18.2% were pre-existing MG exacerbations and 9.1% were exacerbations of subclinical MG. The average onset of symptoms was 5.59 weeks post treatment initiation (range 2–12 weeks). Of these cases, 59% were AChR-Ab positive and 41% were AChR-Ab negative with a survival rate of 84% and 77%, respectively. In addition, nine patients had concurrent elevated CK levels suggestive of myopathy/myositis; however, tissue diagnoses were lacking in all but one case. Of note, the serum CK in those patients resolved in parallel with the resolution of myasthenic symptomatology.

We also noted some intriguing associations with specific immune checkpoint inhibitors:

- Among ten reported cases of pembrolizumab-associated MG, 70% were de novo and 30% were exacerbations. The mean onset of symptoms was 6.95 weeks post initiation of pembrolizumab with a 20% mortality rate. Of note, Brahmer et al. [23] published an additional report of pembrolizumab-induced MG, yet due to the absence of case details, it was not included in the analysis.
- Among seven reported cases of nivolumab-associated MG, 57.1% were de novo, 14.3% were exacerbations, 28.5% were exacerbations of subclinical disease. The mean onset of symptoms was 5.14 weeks post initiation of nivolumab with a 42.9% mortality rate.
- Among four reported cases of ipilimumab-associated MG, all were de novo presentations. The mean onset of symptoms was 4.75 weeks post initiation with a 0% mortality rate.
- Among two reported cases of immune checkpoint inhibitor combination therapy-associated MG, both resulted in mortality.

The hypothesis underpinning the development of de novo MG or exacerbation of this disease with immune checkpoint inhibitors per se has not been formally postulated; however, CTLA-4 may play a pivotal role from an autoimmune perspective [24,25]. Notably, CTLA-4 haploinsufficiency is associated with an autoimmune syndrome affecting multiple organs [26] and specifically, CTLA-4 knockout mice can spontaneously develop MG [27]. Moreover, certain CTLA-4 genetic variants have a predisposing effect on general risk of MG in both Caucasian [28,29] and East Asian populations [30]. With respect to PD-1, its overexpression is associated with favourable outcomes in autoimmune diseases as it potentiates CD8 T-cell exhaustion; hence, it is feasible that PD-1 inhibition could result in the exacerbation of symptoms in patients with pre-existing MG [31,32].

Generally, AChR-Abs are identified in 80–85% of MG patients [33]. However, amongst the 16 cases of de novo MG, there was an equal incidence of AChR-Ab positive and negative patients. In the context of pre-existing MG exacerbations with immune checkpoint inhibitors, the significance of AChR-Abs is unclear, with one of these four patients being AChR-Abs negative. The complexity of this issue is also highlighted in the case of a 59-year-old woman with metastatic melanoma published by Zhu et al. [21]. This patient presented with rapidly progressively hoarseness and dysphagia, eventually requiring the placement of a percutaneous endoscopic gastrostomy tube. Interestingly, her initial diagnosis was made when she was in her 30s with AChR-Abs positive. Yet the AChR-Abs were negative when tested during the event of pembrolizumab-induced MG. Hence, the role of AChR-Abs in immune checkpoint inhibitor-related MG requires further clarification.

Given the severity and potential mortality of MG occurring post immune checkpoint inhibition, it is essential to identify patients who are at risk of developing this phenomenon. As most conventional studies exclude patients with a significant history of autoimmunity, it is difficult to assess the effect of immune checkpoint inhibitors in a large cohort of subjects. In a study of 52 patients with significant autoimmune disorders who proceeded to receive a PD-1 inhibitor, 38% had a flare of their underlying autoimmune disorder [34]. The flares occurred in 60% of patients who began PD-1 inhibition with active disease as compared with 30% of patients who had clinically inactive disease. Flares occurred more often in those who began PD-1 inhibition while on immunosuppressive therapy (50%) as compared with those not on immunosuppression (31%); however, the rate of conventional irAEs was similar to those observed in the clinical trial populations [34].

Interestingly, Zimmer et al. [6] reported an average of 15 weeks elapsing post initiation before patients developing neurological side-effects as a result of anti-PD-1 therapy. Conversely, we found that the average elapsed time before developing MG as a result of immune
checkpoint inhibition was much earlier at 5.8 weeks post initiation. Consequently, a high level of suspicion for the development of MG is most warranted within the first one to four cycles of immune checkpoint inhibition. Furthermore, in most instances after the development of MG, immune checkpoint inhibitor therapy was ceased. However, there were two exceptional cases whereby therapy was continued for five [3] and seven [19] cycles, respectively, after the myasthenic events.

Currently, there are four predominant modalities of treatment for MG: symptomatic treatment (anticholinesterase inhibitors: pyridostigmine), chronic immunomodulating treatment (glucocorticoids and immunosuppressants), rapid immunomodulating treatments (IVIG and plasmapheresis) and surgical treatment (thymectomy). Pyridostigmine is useful for maintenance therapy, yet most patients with MG will require some degree of immunomodulation. Chronic immunomodulating drugs that are available for MG include: prednisone, azathioprine, cyclosporine and mycophenolate mofetil. The side-effects of these immunomodulators are well documented, and hence it is recommended that anticholinesterase inhibitors be used to facilitate the use of a lower dose of immune modulators. Understandably, rapid immunomodulating agents such as plasmapheresis and IVIG can be employed in scenarios such as myasthenic crisis in which ‘rapid’ immunosuppression is required. Finally, thymectomy can be used for patients with non-thymomatous, generalised acetylcholine receptor antibody-associated MG. Yet, the effects of thymectomy take months to years to yield a response. Chang et al. [10] explored the efficacy of the aforementioned treatment options in immune checkpoint inhibitor-associated MG. Consistent with the clinical cases reported, pyridostigmine alone was found to provide minimal benefit unless symptoms were non-progressive and minimal. Intuitively, an escalation of symptoms portends an escalation of treatment. Subsequently, both IVIG and plasmapheresis have been reported to provide a significant clinical reduction in symptoms. Intriguingly, the administration of corticosteroids at a dose of 1 mg/kg daily is associated with a transient deterioration of muscle strength in one-third to one-half of the patients [10]. As a result, steroid-exacerbated muscle weakness can progress to transient respiratory failure, requiring mechanical ventilation in a minority of patients. Owing to this phenomenon, it is recommended that all patients commenced on steroids for immune checkpoint inhibitor-associated MG are hospitalised for regular observations.

8. Conclusion

With the advent of immune checkpoint inhibitors, there have been significant advances in the treatment of a number of malignancies. However, the recognition of timing and treatment of irAEs with these therapies is integral to the clinical management of patients undertaking immunotherapy. Although neurological sequelae of immune checkpoint inhibitors are relatively rare, MG, in particular, is becoming an increasingly recognised phenomenon, with potentially fatal outcomes witnessed in just under a third of the cases reported in the literature. In light of this growing evidence, it is recommended that physicians are cognisant of this toxicity and have a low threshold for aggressive intervention.

Conflict of interest statement

None declared.

References


